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MEETING ABSTRACT

A2.1

Development of theranostic nanosystems on the base of amphiphilic 1,4-dihydropyridines with styrylpyridinium moieties

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Background: The combination of diagnostic and therapeutic properties into the same agent for theranostic purposes now is focussing more and more on multifunctional nanomaterials giving "theranostic nanoparticles" [1]. Pyridinium amphiphiles on 1,4-dihydropyridine (1,4-DHP) scaffold having self-assembling properties, capable to form liposomes can be used for DNA delivery [2,3] or in perspective for drug delivery.

Objectives: The aim of this work is the development of new nanosystems forming molecules which includes: (1) synthesis of new cationic moieties containing amphiphiles; (2) evaluation of biological activities: cytotoxicity, compound-generated reactive oxygen species (ROS) activity and ability to inhibit the calcium channels.

Methods: Cationic 1,4-DHPs were synthesized according to Pajuste *et al.* [3]. Cytotoxicity of 1,4-DHPs *in vitro* was assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay on two monolayer tumour cell lines—HT-1080 and MH-22A in comparison with their action on normal mouse fibroblasts. The Neutral red uptake (NRU) assay was performed on 3T3 cells according to Stokes *et al.* [4]. Data from the *in vitro* tests was used for estimation of the starting dose for acute oral toxicity (LD_{50}) tests in rodents. Effects of total reactive oxygen species production after tested compound exposure in the HT-1080 cell line using CM-H_2DCFDA as a fluorescent probe. Ca^{2+} channel antagonist/agonist activities were assayed by changes of intracellular Ca^{2+} concentrations in A7R5 aorta smooth muscle cells.

Results: This type of compounds is interesting due to self-assembling properties and 1,4-dihydropyridine cycle because the 1,4-DHP moiety acts as an active linker. Establishing structure–activity relationships is a promising tool for design and development of putative theranostic agents. We have synthesized more than thirty pyridinium amphiphiles by targeted modification of 1,4-DHP substituents at 3,5-positions, phenyl substituent at the position 4 and 2,6-pyridinium moieties; compared their cytotoxicities, estimated LD_{50}, ability to inhibit the calcium channels, radical scavenging activity. For all synthesized amphiphiles, evaluation of fluourescence was performed. All fluorescence spectra were recorded with excitation at 410 nm and emission between 400 and 760 nm. All spectra were acquired under identical conditions. Only eight compounds possessed significant fluorescence.

Conclusions: The obtained data confirmed that properties of the synthesized compounds were dependent on the positions and nature of the substituents.

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Keywords: amphiphilic 1,4-dihydropyridines – styrylpyridinium moiety – cytotoxicity – generated ROS activity – Ca^{2+} channel antagonist/agonist

References

1. Fan Z, Fu PP, Yu H, Ray PC: **Theranostic nanomedicine for cancer detection and treatment.** *J Food Drug Anal,* 2014; 22(1):3–17. doi:10.1016/j.jfda.2014.01.001
2. Hyvönen Z, Plotniece A, Reine I, Chekavichus B, Duburs G, Urtti A: **Novel cationic amphiphilic 1,4-dihydropyridine derivatives for DNA delivery.** *Biochim Biophys Acta,* 2000; 1509(1–2):452–456. doi:10.1016/S0005-2736(00)00327-8
3. Pajuste K, Hyvönen Z, Petrichenko O, Kaldre D, Rucins M, Cekavicus B, Ose V, Skrivele B, Gosteva M, Morin-Picardat E, Plotniece M, Sobolev A, Duburs G, Ruponen M, Plotniece A: **Gene delivery agents possessing antiradical activity: self-assembling cationic amphiphilic 1,4-dihydropyridine derivatives.** *New J Chem,* 2013; 37(10):3062–3075. doi:10.1039/C3NJ00272A
4. Stokes WS, Casati S, Strickland J, Paris M: **Neutral red uptake cytotoxicity tests for estimating starting doses for acute oral toxicity tests.** *Curr Protoc Toxicol,* 2008; 36:20.4.1–20.4.20. doi:10.1002/0471140856.tx2004s36